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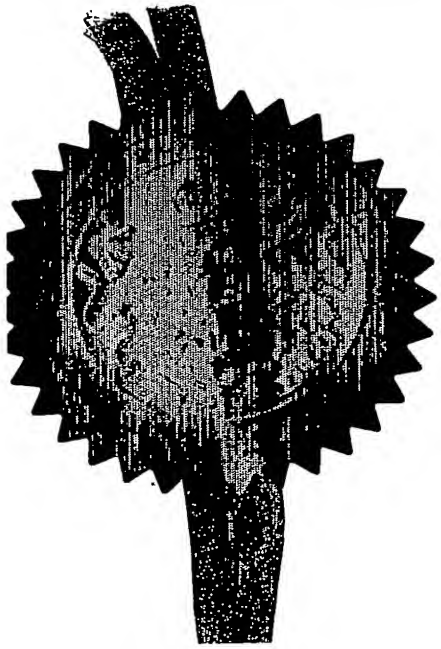

Signed P. Mahoney

Dated 13 January 2004

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P01/7700 0.00-0228490.9

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2. Patent application number *(The Patent Office will fill in this part)* 0228490.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AMERSHAM PLC
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA

Patents ADP number *(if you know it)* 81893750004

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

4. Title of the invention

NOVEL IMAGING COMPOUNDS

5. Name of your agent *(if you have one)*

ROLLINS, Anthony, John; HAMMER, Catriona, MacLeod and HAMMETT, Audrey, Grace, Campbell
Amersham plc
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"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* 81893750004

Patents ADP number *(if you know it)*

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11. I/We request the grant of a patent on the basis of this application.

A.J. Rollins

ROLLINS, Anthony, John

Signature

Date
6 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

BANNAN, Sally
01494 542023

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NOVEL IMAGING COMPOUNDS

Technical Field of the Invention

The present invention relates to the field of *in vivo* diagnostic imaging. In particular the present invention relates to novel imaging agents comprising macrophage scavenger receptor antagonists, said novel imaging agents being useful in *in vivo* diagnostic imaging.

Background and Description of Related Art

Cardiovascular disease (CVD) is the leading cause of death in the Western world and encompasses dysfunctional conditions of the heart, arteries, veins and lungs that supply oxygen to vital life-sustaining areas of the body like the brain, the heart itself, and other vital organs. These conditions include coronary heart disease (CHD), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), atherosclerosis, and thrombosis, and can lead to potentially life-threatening events as myocardial infarction (MI), pulmonary embolism (PE) and stroke. One factor in common to all these conditions is the involvement of macrophages.

CHD is the most prevalent of the cardiovascular diseases. In 1998 it is estimated that CHD was the cause of 7 million deaths worldwide. CAD precedes CHD, and in the majority of cases the underlying cause is atherosclerosis. Atherosclerosis is a benign disease for many decades until the atherosclerotic plaque becomes atheromatous and potentially symptom producing. The plaque can obstruct blood flow resulting in stenosis of the artery, leading to acute myocardial ischemia in the case of coronary arteries. Additionally, mature atherosclerotic plaques can rupture resulting in the release of thrombogenic lipid, and this plaque component can form a thrombosis that completely blocks the artery. Angina is a common manifestation of CHD and is often the forerunner to more serious complications such as acute coronary syndromes including unstable angina, myocardial infarction and sudden cardiac death. Plaque rupture precedes the majority of clinical events and the vulnerability of plaques is the most important predictor of clinical outcome.

Macrophage scavenger receptors (MSRs) are expressed on resident macrophages in tissues such as lung, liver, spleen, and recognise modified forms of low-density lipoprotein (LDL). They are not expressed on circulating cells. Class A MSR (MSRA) is known to have a role in the development of atherosclerotic plaques, MSRA I and MSRA II being responsible for the uptake of oxidised LDL and acetylated LDL into macrophages. MSRA expression is an indicator of the lipid burden of macrophages, and therefore may indicate instability of an atherosclerotic plaque.

A series of MSRA antagonists have been reported as being useful in the treatment of CVD. These include salicylanilide derivatives (WO 99/07382), isophthalic acid derivatives (WO 00/06147), phenylenediamines (WO 00/03704) and sulfonamidobenzanilide derivatives (WO 00/78145 and WO 01/98264). The cited documents disclose pharmaceutical compositions comprising these compounds for the treatment of CVD in humans. In addition to being useful in the treatment of CVD, the cited documents also disclose that these compounds may be used in methods for antagonising the MSRA in animals as well as methods for inhibiting lipid accumulation within macrophage-derived foam cells.

WO 02/067761 discloses detectably labelled MSRA antagonists as being useful in the diagnosis and monitoring of CVD. These MSRA antagonists are salicylanilide derivatives, isophthalic acid derivatives and phenylenediamine derivatives. MSRA antagonists that are sulphonamidobenzamide compounds are not disclosed. The IC_{50} values for the compounds of WO 02/067761 are disclosed as <100mM in binding/uptake assays. No specific examples of particular compounds tested are given in that document. The compounds of the present invention have been shown to display superior binding characteristics.

Summary of the Present Invention

Novel imaging agents comprising synthetic MSRA antagonists have now been identified that possess superior properties over the prior art compounds for diagnosis and monitoring of CVD as well as neurological conditions in which microglia are involved.

An MSRA antagonist is attached to an imaging moiety, said imaging moiety being suitable for the *in vivo* detection of the MSRA antagonist using known diagnostic imaging modalities. Suitable synthetic MSRA antagonists of the present invention are sulphonamidobenzamide compounds. The imaging agents of the invention display superior properties for imaging compared with the prior art compounds.

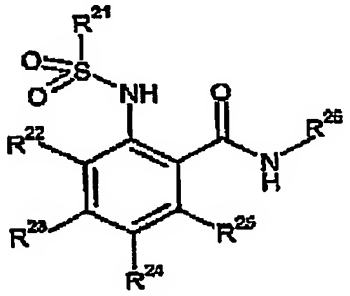
Also disclosed in the present invention is a pharmaceutical composition comprising the novel imaging agent of the present invention and kits for the preparation of said pharmaceutical composition. Furthermore, the present invention discloses a method of imaging CVD using the novel imaging agent of the invention.

Detailed Description of the Invention

The compounds of the invention are useful for diagnostic imaging of CVD. "CVD" as defined in the present invention includes such disease states as atherosclerosis, CAD, thrombosis, transient ischaemia and renal disease. The compounds of the invention are also useful for diagnostic imaging of neurological diseases where microglia are implicated such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and encephalitis.

A first aspect of the invention is an imaging agent which comprises a synthetic MSRA antagonist labelled with an imaging moiety, wherein the synthetic MSRA antagonist is a sulphonamidobenzamide compound, and wherein the imaging moiety can be detected externally in a non-invasive manner following administration of said labelled synthetic MSRA antagonist to the mammalian body *in vivo*.

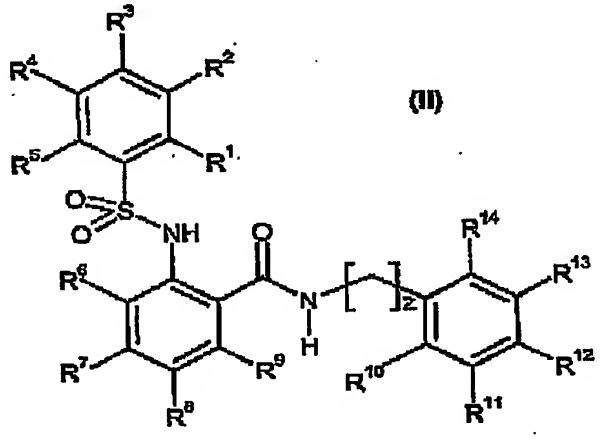
Suitable sulphonamidobenzamide compounds of the invention are of Formula (I):



(I)

wherein R^{21} to R^{26} are independently selected from hydrogen, C_{1-6} alkyl, C_{6-14} aryl, carboxy, amino, hydroxy, or methoxy and wherein one or more of R^{22} to R^{25} may alternatively be a halogen.

A preferred sulphonamidobenzamide compound of the invention is of Formula (II):



(II)

wherein;

z is 0, 1 or 2;

R^1-R^{14} are independently R groups, where R is;

hydrogen, hydroxy, carboxy, C_{1-6} alkyl, nitro, cyano, amino, halogen, C_{6-14} aryl, alkenyl, alkynyl, acyl, aroyl, carboalkoxy, carbamoyl, carbamyl, alkysulphinyl, arylsulphinyl, arylalkylsulphinyl, alkylsulphonyl, arylsulphonyl, arylalkylsulphonyl, sulphamyl, arylsulphonamido or alkylsulphonamido.

A preferred imaging agent of the invention is of Formula (II) wherein each R^1 to R^{14} is chosen from an imaging moiety, hydrogen, C_{1-6} alkyl, hydroxy, carboxy, amino or halogen.

A most preferred imaging agent of the invention is of Formula (II) wherein one of R^2, R^3, R^7, R^8 and R^{12} is an imaging moiety, and the remaining R^2, R^3, R^7, R^8 and R^{12} groups are independently selected from hydrogen, C_{1-6} alkyl, carboxy, or a halogen selected from chlorine, bromine, fluorine or iodine.

An especially preferred imaging agent of the invention is of Formula (II) wherein R^3, R^8 and R^{12} are all halogens with at least one being an imaging moiety.

The sulphonamidobenzamide compounds of the invention can be prepared as described in Scheme 1 of WO 00/78145. An example synthesis is that of a compound of Formula (II) where z = 0 which is illustrated in Figure 1. R^1 to R^{14} are as defined for Formula (II) above. Similar syntheses may be used for the preparation of compounds of Formula (II) wherein z = 1 and z = 2.

"Alkyl" used either alone or as part of another group is defined herein as any straight, branched or cyclic, saturated or unsaturated C_nH_{2n+1} group, wherein unless otherwise specified n is an integer between 1 and 6. The term alkyl in the present invention is also taken to include substituted alkyls, e.g. hydroxyalkyls, haloalkyls, aminoalkyls, carboxyalkyls and alkoxyalkyls.

"Aryl" used either alone or as part of another group is defined herein as any C_{6-14} molecular fragment or group which is derived from a monocyclic or polycyclic aromatic hydrocarbon. Suitable aryl groups of the invention include, but are not limited to, haloaryl, alkylaryl, arylcarbamyl, phenylazo, arylamino, arylthio, toluene, benzoic acid, phenol, arylsulfinyl, arylsulfonyl, arylsulfonamido, benzothiophene, naphthalene, quinoline, isoquinoline, pyridine, pyrimidine, and pyrazine.

The term "halogen" means a group selected from fluorine, chlorine, bromine, and iodine or isotopes thereof.

An "imaging moiety" is defined herein as any group that permits external detection using diagnostic imaging techniques of compounds present *in vivo* to which said imaging moiety is attached. Said imaging moiety may be chosen from:

(i) a radioactive metal ion;
(ii) a paramagnetic metal ion;
(iii) a gamma-emitting radioactive halogen;
(iv) a positron-emitting radioactive non-metal;
(v) a hyperpolarised NMR-active nucleus.

When the imaging moiety is a radioactive metal ion, i.e. a radiometal, suitable radiometals can be either positron emitters such as ^{64}Cu, ^{48}V, ^{52}Fe, ^{55}Co, ^{94m}Tc or ^{68}Ga; or γ-emitters such as ^{99m}Tc, ^{111}In, ^{113m}In, ^{67}Cu or ^{67}Ga. Preferred radiometals are ^{99m}Tc, ^{64}Cu, ^{68}Ga and ^{111}In. Most preferred radiometals are γ-emitters, especially ^{99m}Tc.

When the imaging moiety is a paramagnetic metal ion, suitable such metal ions include: Gd(III), Mn(II), Cu(II), Cr(III), Fe(III), Co(II), Er(II), Ni(II), Eu(III) or Dy(III). Preferred paramagnetic metal ions are Gd(III), Mn(II) and Fe(III), with Gd(III) being especially preferred.

When the imaging moiety is a positron-emitting radioactive non-metal, suitable such positron emitters include ^{11}C, ^{13}N, ^{15}O, ^{17}F, ^{18}F, ^{75}Br, ^{76}Br and ^{124}I. Preferred positron-emitting radioactive non-metals are ^{11}C, ^{13}N and ^{18}F, especially ^{11}C and ^{18}F, most especially ^{18}F.

When the imaging moiety is a gamma-emitting radioactive halogen, the radiohalogen is suitably chosen from ^{77}Br or a gamma-emitting radioactive isotope of iodine, preferably ^{123}I or ^{131}I. A most preferred gamma-emitting radioactive halogen is ^{123}I.

When the detectable moiety is a hyperpolarised NMR-active nucleus, such NMR-active nuclei have a non-zero nuclear spin, and include ^{13}C, ^{15}N, ^{19}F, ^{29}Si and ^{31}P. Of these, ^{13}C is preferred. By the term "hyperpolarised" is meant enhancement of the degree of polarisation of the NMR-active nucleus over its' equilibrium polarisation. The natural abundance of ^{13}C (relative to ^{12}C) is about 1%, and suitable ^{13}C-labelled compounds are suitably enriched to an abundance of at least 5%, preferably at least 50%, most preferably at least 90% before being hyperpolarised. At least one carbon atom of the MSRA antagonist of the present invention is suitably enriched with ^{13}C, which is subsequently hyperpolarised.

Whichever imaging moiety is selected from the above, it is preferably reacted with a precursor of said imaging agent. Reaction of such a precursor with a suitable chemical form of the imaging moiety results in the production of said imaging agent. A "precursor" as defined in the present invention is a MSRA antagonist compound to which an imaging moiety may be readily attached, preferably in a one-step process. One example of a suitable precursor of the invention is a MSRA antagonist conjugated to a metal chelating agent, suitable for the attachment of an imaging moiety which is a metal ion. Another example of a suitable precursor of the invention is a MSRA antagonist that includes a group such as (a) a non-radioactive halogen atom, (b) an activated aryl ring, (c) an organometallic precursor compound, or (d) an organic precursor such as triazene. Such a precursor is suitable for the incorporation of an imaging moiety which is a radioactive halogen. These precursor compounds and the resultant imaging agents are described more fully in the following sections.

When the imaging moiety comprises a metal ion, the metal ion is suitably attached to the MSRA antagonist as part of a conjugate of Formula (III):

[{MSRA antagonist}-$(L)_x$]$_y$-[metal complex] (III)

wherein:

$(L)_x$ is a linker group;

x is an integer of value 0 to 10;

y is 1, 2 or 3.

By the term "metal complex" is meant a coordination complex of the metal ion with one or more ligands. It is strongly preferred that the metal complex is "resistant to transchelation", i.e. does not readily undergo ligand exchange with other potentially competing ligands for the metal coordination sites. Potentially competing ligands include the synthetic MSRA antagonist itself plus other excipients in the preparation *in vitro* (e.g. radioprotectants or antimicrobial preservatives used in the preparation), or endogenous compounds *in vivo* (e.g. glutathione, transferrin or plasma proteins). The "linker group" $(L)_x$ is as defined below for Formula (IIIa).

The metal complexes of Formula (III) are conveniently prepared from precursors which are ligand conjugates of Formula (IIIa):

[{MSRA antagonist}-$(L)_x$]$_y$-[ligand] **(IIIa)**

where:

-$(L)_x$- is a linker group wherein each L is independently -CZ_2-, -CZ=CZ-, -C≡C-, -CZ_2CO_2-, -CO_2CZ_2-, -NZCO-, -CONZ-, -NZ(C=O)NZ-, -NZ(C=S)NZ-, -SO_2NZ-, -$NZSO_2$-, -CZ_2OCZ_2-, -CZ_2SCZ_2-, -CZ_2NZCZ_2-, a C_{4-8} cycloheteroalkylene group, a C_{4-8} cycloalkylene group, a C_{5-12} arylene group, or a C_{3-12} heteroarylene group;

Z is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl;

x is an integer of value 0 to 10; and

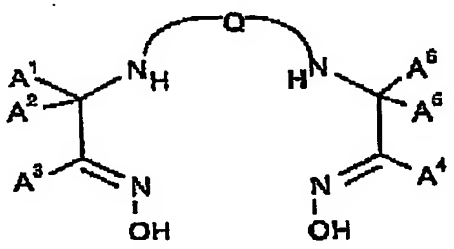
y is 1, 2 or 3.

In Formulae (III) and (IIIa), y is preferably 1 or 2, and is most preferably 1.

Suitable ligands for use in the present invention, which form metal complexes resistant to transchelation, include chelating agents which have 2-6, preferably 2-4, metal donor atoms arranged such that 5- or 6-membered chelate rings result (by having a non-coordinating backbone of either carbon atoms or non-coordinating heteroatoms linking the metal donor atoms). Examples of donor atom types which bind well to metals as part of chelating agents are: amines, thiols, amides, oximes and phosphines. Phosphines form such strong metal complexes that even monodentate or bidentate phosphines form suitable metal complexes. The linear geometry of isonitriles and diazenides is such that they do not lend themselves readily to incorporation into chelating agents, and are hence typically used as monodentate ligands. Examples of suitable isonitriles include simple alkyl isonitriles such as *tert*-butylisonitrile, and ether-substituted isonitriles such as MIBI (i.e. 1-isocyano-2-methoxy-2-methylpropane). Examples of suitable phosphines include Tetrofosmin, and monodentate phosphines such as *tris*(3-methoxypropyl)phosphine. Examples of suitable diazenides include the HYNIC series of ligands, i.e. hydrazine-substituted pyridines or nicotinamides.

Examples of suitable chelating agents for technetium which form metal complexes resistant to transchelation include, but are not limited to:

(i) diaminedioximes of Formula (IV):



(IV)

where A^1-A^6 are each independently an A group;

each A is H or C_{1-10} alkyl, C_{3-10} alkylaryl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} fluoroalkyl, C_{2-10} carboxyalkyl or C_{1-10} aminoalkyl, or two or more A groups together with the atoms to which they are attached form a carbocyclic, heterocyclic, saturated or

unsaturated ring, and wherein one or more of the A groups is conjugated to the MSRA antagonist;

and Q is a bridging group of Formula $-(J)_m-$;

where m is 3, 4 or 5 and each J is independently -O-, -NA- or $-C(A)_2-$ provided that $-(J)_m-$ contains a maximum of one J group which is -O- or -NA-.

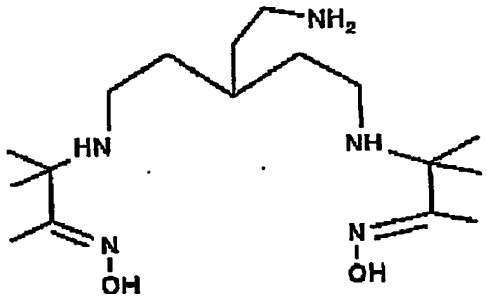
Preferred Q groups are as follows:

$Q = -(CH_2)(CHA)(CH_2)-$ i.e. propyleneamine oxime or PnAO derivatives;
$Q = -(CH_2)_2(CHA)(CH_2)_2-$ i.e. pentyleneamine oxime or PentAO derivatives;
$Q = -(CH_2)_2NA(CH_2)_2-$.

A^1 to A^6 are preferably chosen from: C_{1-3} alkyl, alkylaryl alkoxyalkyl, hydroxyalkyl, fluoroalkyl, carboxyalkyl or aminoalkyl. Most preferably, each A^1 to A^6 group is CH_3.

The synthetic MSRA antagonist is preferably conjugated at either A^1 or A^6, or an A group of the Q moiety. Most preferably, the MSRA antagonist is conjugated to an A group of the Q moiety. When the MSRA antagonist is conjugated to an A group of the Q moiety, the A group is preferably at the bridgehead position. In that case, Q is preferably $-(CH_2)(CHA)(CH_2)-$, $-(CH_2)_2(CHA)(CH_2)_2-$ or $-(CH_2)_2(NA)(CH_2)_2-$, most preferably $-(CH_2)_2(CHA)(CH_2)_2-$.

An especially preferred bifunctional diaminedioxime chelator is of Formula (V):



(V)

such that the synthetic MSRA antagonist is conjugated *via* the bridgehead NH_2 group. This chelator will also be referred to as "chelating agent 1".

(ii) N_3S ligands having a thioltriamide donor set such as MAG_3 and related ligands; or having a diamidepyridinethiol donor set such as PICA;

(iii) N_2S_2 ligands having a diaminedithiol donor set such as BAT or ECD (i.e. ethylcysteinate dimer), or an amideaminedithiol donor set such as MAMA;

(iv) N_4 ligands which ore open chain or macrocyclic ligands having a tetramine, amidetriamine or diamidediamine donor set, such as cyclam, monoxocyclam or dioxocyclam; and,

(v) N_2O_2 ligands having a diaminediphenol donor set.

The above described ligands are particularly suitable for complexing technetium, e.g. ^{94m}Tc or ^{99m}Tc, and are described more fully by Jurisson *et al* [Chem.Rev., 99, 2205-2218 (1999)]. The ligands are also useful for other metals, such as copper (^{64}Cu or ^{67}Cu), vanadium (e.g. ^{48}V), iron (e.g. ^{52}Fe), or cobalt (e.g. ^{55}Co). Other suitable ligands are described in Sandoz WO 91/01144, which includes ligands which are particularly suitable for indium, yttrium and gadolinium, especially macrocyclic aminocarboxylate and aminophosphonic acid ligands. Ligands which form non-ionic (i.e. neutral) metal complexes of gadolinium are known and are described in US 4885363. When the radiometal ion is technetium, the ligand is preferably a chelating agent which is tetradentate. Preferred chelating agents for technetium are the diaminedioximes, or those having an N_2S_2 or N_3S donor set as described above. Especially preferred chelating agents for technetium are the diaminedioximes.

It is envisaged that the role of the linker group $-(L)_x-$ in Formula (III) and (IIIa) is to distance the relatively bulky metal complex which results upon metal co-ordination, from the active site of the MSRA antagonist, so that binding of the antagonist to MSRA is not impaired. This can be achieved by a combination of flexibility (e.g. simple alkyl chains),

so that the bulky group has the freedom to position itself away from the active site and/or rigidity such as a cycloalkyl or aryl spacer which orientates the metal complex away from the active site.

The nature of the linker group can also be used to modify the biodistribution of the resulting metal complex of the conjugate. Thus, e.g. the introduction of ether groups in the linker will help to minimise plasma protein binding. Preferred linker groups have a backbone chain of linked atoms which make up the $(L)_x$ moiety containing 2 to 10 atoms, most preferably 2 to 5 atoms, with 2 or 3 atoms being especially preferred. A minimum linker group backbone chain of 2 atoms confers the advantage that the ligand is well-separated from the MSRA antagonist so that any interaction is minimised.

Non-peptide linker groups such as alkylene groups or arylene groups have the advantage that there are no significant hydrogen bonding interactions with the conjugated MSRA antagonist, so that the linker does not wrap round onto the MSRA antagonist. Preferred alkylene spacer groups are $(CH_2)_q$ where q is 2 to 6. Preferred arylene spacers are of Formula (VI):

(VI)

where: a and b are independently 0, 1 or 2.

It is strongly preferred that the metal complex is bound in such a way that the linkage does not undergo facile metabolism in blood, since that would result in the metal complex being cleaved off before the imaging agent reaches the desired *in vivo* target site. The metal complexes are preferably covalently bound *via* linkages which are not readily metabolised.

When the imaging moiety is a radioactive halogen, it is preferably a radioactive isotope of iodine. The radioiodine atom is preferably attached *via* a direct covalent bond to an

aromatic ring such as a benzene ring, or a vinyl group since it is known that iodine atoms bound to saturated aliphatic systems are prone to *in vivo* metabolism and hence loss of the imaging moiety.

When the imaging moiety is radioactive halogen, such as iodine, suitable precursors of the imaging agent include: a non-radioactive halogen atom such as an aryl iodide or aryl bromide (to permit radioiodine exchange); an activated aryl ring (e.g. a phenol group); or an organometallic precursor compound (e.g. trialkyltin or trialkylsilyl), an organic precursor such as triazenes or other such moiety known to those skilled in the art. Methods of introducing radioactive halogens (including ^{123}I and ^{18}F) are described by Bolton [J.Lab.Comp.Radiopharm., 45, 485-528 (2002)].

Examples of suitable aryl groups to which radioactive halogens, especially iodine can be attached are given below:

Both contain substituents which permit facile radioiodine substitution onto the aromatic ring. Alternative substituents containing radioactive iodine can be synthesised by direct iodination, e.g. *via* radiohalogen exchange:

In a second aspect of the invention a pharmaceutical composition comprising the imaging agent of the invention together with a biocompatible carrier, in a form suitable for mammalian administration, is disclosed.

A "pharmaceutical composition" is defined in the present invention as a formulation comprising the imaging agent of the invention or a salt thereof in a form suitable for administration to humans. The pharmaceutical composition of the invention is

preferably administered parenterally, i.e. by injection, and most preferably as an aqueous solution. Such a formulation may optionally contain further ingredients such as buffers; pharmaceutically acceptable solubilisers (e.g. cyclodextrins or surfactants such as Pluronic, Tween or phospholipids); pharmaceutically acceptable stabilisers or antioxidants (such as ascorbic acid, gentisic acid or *para*-aminobenzoic acid).

In a third aspect of the invention, a kit for the preparation of the pharmaceutical composition of the invention is disclosed which comprises a precursor of the imaging agent of the invention. Such kits are designed to give sterile products suitable for human administration, e.g. *via* direct injection into the bloodstream, and comprise a precursor of said imaging agent.

Preferably, the kit is for the preparation of a pharmaceutical composition which comprises an imaging agent wherein the imaging moiety is selected from a radioactive metal ion, a paramagnetic metal ion, or a radiohalogen. The precursor in each case is as described earlier in the description, e.g. Formula (IIIa) for metal ions.

Where the radiometal is ^{99m}Tc, the kit is preferably lyophilised and is designed to be reconstituted with sterile ^{99m}Tc-pertechnetate (TcO_4^-) from a ^{99m}Tc radioisotope generator to give a solution suitable for human administration without further manipulation. Suitable kits comprise a container (e.g. a septum-sealed vial) containing the MSRA antagonist-chelating agent conjugate in either free base or acid salt form, together with a pharmaceutically acceptable reducing agent such as sodium dithionite, sodium bisulphite, ascorbic acid, formamidine sulphinic acid, stannous ion, Fe(II) or Cu(I). The pharmaceutically acceptable reducing agent is preferably a stannous salt such as stannous chloride or stannous tartrate. Alternatively, the kit may optionally contain a metal complex, which upon addition of the radiometal, undergoes transmetallation (i.e. metal exchange) giving the desired product.

Kits for the preparation of the imaging agents of the invention may optionally further comprise additional components such as a transchelator, radioprotectant, antimicrobial preservative, pH-adjusting agent or filler. The "transchelator" is a compound which

reacts rapidly to form a weak complex with technetium, then is displaced by the diaminedioxime. This minimises the risk of formation of reduced hydrolysed technetium (RHT) due to rapid reduction of pertechnetate competing with technetium complexation. Suitable such transchelators are salts of a weak organic acid, i.e. an organic acid having a pKa in the range 3 to 7, with a biocompatible cation. Suitable such weak organic acids are acetic acid, citric acid, tartaric acid, gluconic acid, glucoheptonic acid, benzoic acid, phenols or phosphonic acids. Hence, suitable salts are acetates, citrates, tartrates, gluconates, glucoheptonates, benzoates, phenolates or phosphonates. Preferred such salts are tartrates, gluconates, glucoheptonates, benzoates, or phosphonates, most preferably phosphonates, most especially diphosphonates. A preferred such transchelator is a salt of MDP, i.e. methylenediphosphonic acid, with a biocompatible cation.

By the term "radioprotectant" is meant a compound which inhibits degradation reactions, such as redox processes, by trapping highly-reactive free radicals, such as oxygen-containing free radicals arising from the radiolysis of water. The radioprotectants of the present invention are suitably chosen from: ascorbic acid, *para*-aminobenzoic acid (i.e. 4-aminobenzoic acid), gentisic acid (i.e. 2,5-dihydroxybenzoic acid) and salts thereof with a biocompatible cation as described above.

By the term "antimicrobial preservative" is meant an agent which inhibits the growth of potentially harmful micro-organisms such as bacteria, yeasts or moulds. The antimicrobial preservative may also exhibit some bactericidal properties, depending on the dose. The main role of the antimicrobial preservative(s) of the present invention is to inhibit the growth of any such micro-organism in the pharmaceutical composition post-reconstitution, i.e. in the imaging agent itself. The antimicrobial preservative may, however, also optionally be used to inhibit the growth of potentially harmful micro-organisms in one or more components of the kit of the present invention prior to reconstitution. Suitable antimicrobial preservative(s) include: the parabens, i.e. methyl, ethyl, propyl or butyl paraben or mixtures thereof; benzyl alcohol; phenol; cresol; cetrimide and thiomersal. Preferred antimicrobial preservative(s) are the parabens.

The term "pH-adjusting agent" means a compound or mixture of compounds useful to ensure that the pH of the reconstituted kit is within acceptable limits (approximately pH 4.0 to 10.5) for human or mammalian administration. Suitable such pH-adjusting agents include pharmaceutically acceptable buffers, such as tricine, phosphate or TRIS [i.e. *tris*(hydroxymethyl)aminomethane], and pharmaceutically acceptable bases such as sodium carbonate, sodium bicarbonate or mixtures thereof. When the MSRA antagonist-chelating agent conjugate is employed in acid salt form, the pH adjusting agent may optionally be provided in a separate vial or container, so that the user of the kit can adjust the pH as part of a multi-step procedure.

By the term "filler" is meant a pharmaceutically acceptable bulking agent which may facilitate material handling during production and lyophilisation. Suitable fillers include inorganic salts such as sodium chloride, and water soluble sugars or sugar alcohols such as sucrose, maltose, mannitol or trehalose.

A fourth aspect of the present invention is the use of the pharmaceutical composition of the invention for the diagnostic imaging of CVD. Preferably, the pharmaceutical composition of the invention may be used in the diagnostic imaging of atherosclerotic plaques, coronary artery disease, thrombosis, transient ischaemia or renal disease. Most preferably, the pharmaceutical composition of the invention may be used in the diagnostic imaging of atherosclerotic plaques. An especially preferred use of the pharmaceutical composition of the invention is for the diagnostic imaging of unstable atherosclerotic plaques.

A further use of the pharmaceutical composition of the invention is in the diagnostic imaging of neurological diseases in which microglial cells are involved, such as Alzheimer's disease, multiple sclerosis, Parkinson's disease and encephalitis.

Examples

Various embodiments of the invention are described in the following non-limiting examples. Example 1 relates to the synthesis of chelating agent 1, which is then used

in the preparation of precursor 1 in Example 2. Precursor 1 is a compound suitable for the attachment of a metal ion, preferably ^{99m}Tc, the attachment of which is described in Example 3. Example 4 describes the synthesis of precursor 2, a compound which is suitable for straightforward substitution with radiohalogen. The process of radiohalogenating precursor 2 to form imaging agent 2 is described in Example 5. Examples 6 and 7 describe a method of preparing a ^{18}F compound of the invention. Example 8 outlines the method used to assess the binding characteristics of compounds of the invention. IC50 values of <40μM for were found in this binding assay for the compounds of the invention.

Example 1: Synthesis of chelating agent 1

Step 1(a): 3(methoxycarbonylmethylene)glutaric acid dimethylester

Carbomethoxymethylenetriphenylphosphorane (167g, 0.5mol) in toluene (600ml) was treated with dimethyl 3-oxoglutarate (87g, 0.5mol) and the reaction heated to 100°C on an oil bath at 120°C under an atmosphere of nitrogen for 36h. The reaction was then concentrated *in vacuo* and the oily residue triturated with 40/60 petrol ether/diethylether 1:1, 600ml. Triphenylphosphine oxide precipitated out and the supernatant liquid was decanted/filtered off. The residue on evaporation *in vacuo* was Kugelrohr distilled under high vacuum Bpt (oven temperature 180-200°C at 0.2torr) to give 3(methoxycarbonylmethylene)glutaric acid dimethylester in 89.08g, 267mM, 53%.

NMR $^1H(CDCl_3)$: δ 3.31 (2H, s, CH_2), 3.7(9H, s, 3xOCH_3), 3.87 (2H, s, CH_2), 5.79 (1H, s, =CH,) ppm.

NMR $^{13}C(CDCl_3)$, δ 36.56,CH_3, 48.7, 2xCH_3, 52.09 and 52.5 (2xCH_2); 122.3 and 146.16 C=CH; 165.9, 170.0 and 170.5 3xCOO ppm.

Step 1(b): Hydrogenation of 3-(methoxycarbonylmethylene)glutaric acid dimethylester.

3(methoxycarbonylmethylene)glutaric acid dimethylester (89g, 267mmol) in methanol (200ml) was shaken with (10% palladium on charcoal: 50% water) (9 g) under an atmosphere of hydrogen gas (50 psi) for (30h). The solution was filtered through kieselguhr and concentrated in vacuo to give 3-(methoxycarbonylmethyl)glutaric acid dimethylester as an oil yield (84.9g, 94 %).

NMR $^1H(CDCl_3)$, δ (12H, m, 4xCH_3), (2H, m, 2xCH_2) (1H, hextet, CH) 3.7 (1H, doublet, CH), (8H, 2 quartets, 4xCH_2O).

NMR $^{13}C(CDCl_3)$, δ and $2xCH_3$, CH, 2xCH2, CH; and $2xCH_2$-O, 168.2 and 171.5 2xCOO.

Step 1(c): Reduction and esterification of trimethyl ester to the triacetate.

Under an atmosphere of nitrogen in a 3 necked 2L round bottomed flask lithium aluminium hydride (20g, 588mmol) in tetrahydrofuran (400ml) was treated cautiously with tri(methyloxycarbonylmethyl)methane (40g, 212mmol) in tetrahydrofuran (200ml) over 1h. A strongly exothermic reaction occurred, causing the solvent to reflux strongly. The reaction was heated on an oil bath at 90°C at reflux for 3 days. The reaction was quenched by the cautious dropwise addition of acetic acid (100ml) until the evolution of hydrogen ceased. The stirred reaction mixture was cautiously treated with acetic anhydride solution (500ml) at such a rate as to cause gentle reflux. The flask was equipped for distillation and stirred and then heating at 90°C (oil bath temperature) to distil out the tetrahydrofuran. A further portion of acetic anhydride (300ml) was added, the reaction returned to reflux configuration and stirred and heated in an oil bath at 140°C for 5h. The reaction was allowed to cool and filtered. The aluminium oxide precipitate was washed with ethyl acetate and the combined filtrates concentrated on a rotary evaporator at a water bath temperature of 50°C *in vacuo* (5 mmHg) to afford an oil. The oil was taken up in ethyl acetate (500ml) and washed with saturated aqueous potassium carbonate solution. The ethyl acetate solution was separated, dried over sodium sulphate, and concentrated *in vacuo* to afford an oil. The oil was Kugelrohr distilled in high vacuum to give *tris*(2-acetoxyethyl)methane (45.313g, 95.9% yield, 0.165 mol) as an oil. Bp. 220 at 0.1 mmHg.

NMR $^1H(CDCl_3)$, δ 1.66(7H, m, $3xCH_2$, CH), 2.08(1H, s, $3xCH_3$); 4.1(6H, t $3xCH_2O$).

NMR $^{13}C(CDCl_3)$, δ 20.9, CH_3; 29.34, CH; 32.17, CH_2; 62.15, CH_2O; 171, CO.

Step 1(d): Removal of Acetate groups from the triacetate.

Tris(2-acetoxyethyl)methane (45.3g, 165mM) in methanol (200ml) and 880 ammonia (100ml) was heated on an oil bath at 80°C for 2 days. The reaction was treated with a further portion of 880 ammonia (50ml) and heated at 80°C in an oil bath for 24h. A further portion of 880 ammonia (50ml) was added and the reaction heated at 80°C for 24h. The reaction was then concentrated *in vacuo* to remove all solvents to give an oil.

This was taken up into 880 ammonia (150ml) and heated at 80°C for 24h. The reaction was then concentrated *in vacuo* to remove all solvents to give an oil. Kugelrohr distillation gave acetamide bp 170-180 0.2mm. The bulbs containing the acetamide were washed clean and the distillation continued. *Tris*(2-hydroxyethyl)methane (22.53g, 152mmol, 92.1%) distilled at bp 220 °C 0.2mm.

NMR $^{1}H(CDCl_3)$, δ 1.45(6H, q, $3xCH_2$), 2.2(1H, quintet, CH); 3.7(6H, t $3xCH_2OH$); 5.5(3H, brs, 3xOH).

NMR $^{13}C(CDCl_3)$, δ 22.13, CH; 33.95, $3xCH_2$; 57.8, $3xCH_2OH$.

Step 1(e): Conversion of the triol to the *tris*(methanesulphonate).

To an stirred ice-cooled solution of *tris*(2-hydroxyethyl)methane (10g, 0.0676mol) in dichloromethane (50ml) was slowly dripped a solution of methanesulphonyl chloride (40g, 0.349mol) in dichloromethane (50ml) under nitrogen at such a rate that the temperature did not rise above 15°C. Pyridine (21.4g, 0.27mol, 4eq) dissolved in dichloromethane (50ml) was then added drop-wise at such a rate that the temperature did not rise above 15°C, exothermic reaction. The reaction was left to stir at room temperature for 24h and then treated with 5N hydrochloric acid solution (80ml) and the layers separated. The aqueous layer was extracted with further dichloromethane (50ml) and the organic extracts combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to give *tris*(2-(methylsulphonyloxy)ethyl)methane contaminated with excess methanesulphonyl chloride. Theoretical yield was 25.8g.

NMR $^{1}H(CDCl_3)$, δ 4.3 (6H, t, $2xCH_2$), 3.0 (9H, s, $3xCH_3$), 2 (1H, hextet, CH,), 1.85 (6H, q, $3xCH_2$).

Step 1(f): Preparation of 1,1,1-*tris*(2-azidoethyl)methane.

A stirred solution of *tris*(2-(methylsulphonyloxy)-ethyl)methane [from step 1(e), contaminated with excess methylsulphonyl chloride] (25.8g, 67mmol, theoretical) in dry DMF (250ml) under nitrogen was treated with sodium azide (30.7g, 0.47mol) portion-wise over 15 minutes. An exotherm was observed and the reaction was cooled on an ice bath. After 30 minutes, the reaction mixture was heated on an oil bath at 50°C for 24h. The reaction became brown in colour. The reaction was allowed to cool, treated with dilute potassium carbonate solution (200ml) and extracted three times with 40/60

petrol ether/diethylether 10:1 (3x150ml). The organic extracts were washed with water (2x150ml), dried over sodium sulphate and filtered. Ethanol (200ml) was added to the petrol/ether solution to keep the triazide in solution and the volume reduced *in vacuo* to no less than 200ml. Ethanol (200ml) was added and reconcentrated *in vacuo* to remove the last traces of petrol leaving no less than 200ml of ethanolic solution.

CARE: DO NOT REMOVE ALL THE SOLVENT AS THE AZIDE IS POTENTIALLY EXPLOSIVE AND SHOULD BE KEPT IN DILUTE SOLUTION AT ALL TIMES.

NMR $^1H(CDCl_3)$, δ 3.35 (6H, t, $3xCH_2$), 1.8 (1H, hextet, CH,), 1.6 (6H, q, $3xCH_2$).

Step 1(g): Preparation of 1,1,1-*tris*(2-aminoethyl)methane.

Tris(2-azidoethyl)methane (15.06g, 0.0676 mol), (assuming 100% yield from previous reaction) in ethanol (200ml) was treated with 10% palladium on charcoal (2g, 50% water) and hydrogenated for 12h. The reaction vessel was evacuated every 2 hours to remove nitrogen evolved from the reaction and refilled with hydrogen. A sample was taken for NMR analysis to confirm complete conversion of the triazide to the triamine. Caution: unreduced azide could explode on distillation. The reaction was filtered through a celite pad to remove the catalyst and concentrated in vacuo to give *tris*(2-aminoethyl)methane as an oil. This was further purified by Kugelrohr distillation bp.180–200°C at 0.4mm/Hg to give a colourless oil (8.1g, 55.9 mmol, 82.7% overall yield from the triol).

NMR $^1H(CDCl_3)$, 2.72 (6H, t, $3xCH_2N$), 1.41 (H, septet, CH), 1.39 (6H, q, $3xCH_2$).

NMR $^{13}C(CDCl_3)$, δ 39.8 (CH_2NH_2), 38.2 (CH_2), 31.0 (CH).

Step 1(h): Synthesis of bis[N-(1,1-dimethyl-2-N-hydroxyimine propyl)2-aminoethyl]-(2-aminoethyl) methane (chelating agent 1).

To a solution of *tris*(2-aminoethyl)methane (4.047g, 27.9mmol) in dry ethanol (30ml) was added potassium carbonate anhydrous (7.7g, 55.8mmol, 2eq) at room temperature with vigorous stirring under a nitrogen atmosphere. A solution of 3-chloro-3-methyl-2-nitrosobutane (7.56g, 55.8mol, 2eq) was dissolved in dry ethanol (100ml) and 75ml of this solution was dripped slowly into the reaction mixture. The reaction was followed by TLC on silica run in dichloromethane, methanol, concentrated (0.88sg) ammonia;

100/30/5 and the TLC plate developed by spraying with ninhydrin and heating. The mono, di and tri alkylated products were seen with RF's increasing in that order. Analytical HPLC was run using RPR reverse phase column in a gradient of 7.5-75% acetonitrile in 3% aqueous ammonia. The reaction was concentrated *in vacuo* to remove the ethanol and resuspended in water (110ml). The aqueous slurry was extracted with ether (100ml) to remove some of the trialkylated compound and lipophilic impurities leaving the mono and desired dialkylated product in the water layer. The aqueous solution was buffered with ammonium acetate (2eq, 4.3g, 55.8mmol) to ensure good chromatography. The aqueous solution was stored at 4°C overnight before purifying by automated preparative HPLC.

Yield (2.2g, 6.4mM, 23%).

Mass spec; Positive ion 10 V cone voltage. Found: 344; calculated M+H= 344.

NMR ^{1}H($CDCl_3$), δ 1.24(6H, s, 2xCH_3), 1.3(6H, s, 2xCH_3), 1.25-1.75(7H, m, 3xCH_2,CH), (3H, s, 2xCH_2), 2.58 (4H, m, CH_2N), 2.88(2H, t CH_2N_2), 5.0 (6H, s, NH_2 , 2xNH, 2xOH).

NMR ^{1}H ($(CD_3)_2SO$) δ1.1 4xCH; 1.29, 3xCH_2; 2.1 (4H, t, 2xCH_2);

NMR ^{13}C($(CD_3)_2SO$), δ 9.0 (4xCH_3), 25.8 (2xCH_3), 31.0 2xCH_2, 34.6 CH_2, 56.8 2xCH_2N; 160.3, C=N.

HPLC conditions: flow rate 8ml/min using a 25mm PRP column

A=3% ammonia solution (sp.gr = 0.88) /water.

B=Acetonitrile

Time	%B
0	7.5
15	75.0
20	75.0
22	7.5
30	7.5

Load 3ml of aqueous solution per run, and collect in a time window of 12.5-13.5 min.

Example 2: Attachment of chelating agent 1 to 4-carboxy-N-(4-bromophenyl)-2-(4-chlorophenylsulfonylamido) benzamide to form precursor 1

Chelating agent 1 was attached to 4-carboxy-N-(4-bromophenyl)-2-(4-chlorophenylsulfonylamido) benzamide by means of Step 1 of the reaction scheme depicted in Figure 2.

To a solution of 4-carboxy-N-(4-bromophenyl)-2-(4-chlorophenylsulfonylamido) benzamide (1mg) in dichloromethane (2ml) at room temperature was added 4 equivalents of TBTU and 1.1 equivalent of the chelating agent of Formula (V), and 3 equivalents of N,N-diisopropylethylamine (DIEA) under a nitrogen atmosphere for 24 hours. The crude mixture was purified by HPLC. Mass Spectrometry analysis: ES [M+H] *m/z* 836.

Example 3: ^{99m}Tc labelling of precursor 1 to form imaging agent 1

Imaging agent 1 is prepared by labelling precursor 1 with ^{99m}Tc according to Step 2 of the reaction scheme depicted in Figure 2.

A $SnCl_2$/MDP solution is prepared by dissolving 10mg $SnCl_2$ and 90mg MDP in 100ml of nitrogen-purged saline. To 50µl 1mg/ml in methanol of precursor 1, is added; (1) 0.7ml methanol, (2) 0.5ml 0.1M sodium carbonate buffer, (3) 0.5ml 500MBq/ml TcO_4, and (4) 100µl of the $SnCl_2$/MDP solution. This reaction mixture is heated at 37°C for 30min to form imaging agent 1.

Example 4: Synthesis of precursor 2

Step 1 of the reaction scheme depicted in Figure 3 is used to prepare precursor 2. 4-*n*-tributyltin aniline is coupled to 5-bromo-2-(4-chlorophenylsulfonamido) benzoic acid in DCM in the presence of 1.5 equivalents of triethylamine to give precursor 2.

Example 5: Radioiodination of precursor 2 to form imaging agent 2

Radioiodination of precursor 2 to form imaging agent 2 is carried out according to Step 2 of the scheme depicted in Figure 3.

10 µM of precursor 2 is reacted with 0.05 mL NaI solution [approx. 0.167 µM total radioiodine (I*)] in the presence of 0.4 mL DMF, 0.1 mL ammonium acetate buffer (pH 4, 0.2 M) and 0.05 mL Chloramine-T solution (0.22 µM). 0.5 mL H_2O is added after 5

minutes. The crude mixture is subsequently separated by HPLC to yield pure imaging agent 2.

Any gamma-emitting radioactive isotope of iodine may be used to produce radiolodinated compounds of the invention, but ^{123}I or ^{131}I are preferred.

Example 6: Synthesis of precursor 3

In Step 1 of the reaction scheme illustrated in Figure 4, 3-chloro-4-nitrobenzenesulfonic acid is reacted with $POCl_3$ to form 3-chloro-4-nitrobenzenesulfonyl chloride, which is reacted with N-(4-bromophenyl)-2-amino-5-bromobenzamide to form 4-bromo-N-(4-bromophenyl)-2-(3-chloro- 4-nitro- phenyl sulphonamido) benzamide (Step 2). The nitro group is then reduced with $SnCl_2.2H_2O$ to yield the amine (Step 3). The amine is then converted into the diazonium compound by treatment with nitrous acid (HONO) in Step 4.

Example 7: Synthesis of imaging agent 3

In Step 5 of the scheme illustrated in Figure 4 $^{18}F^-$ is reacted with the diazonium compound to give imaging agent 3.

Example 8: Scavenger receptor binding assay

An assay was developed based on that described in Lysko *et al.* (1999) J. Pharmacol. Exp. Ther. 289 (3): 1277-1285. The cells used in the assay were either mouse J774.1 or human THP-1. J774.1 cells were seeded at $1x10^5$ cells/well/ml 24 hours prior to assay in Dulbecco's minimum essential medium containing penicillin/streptomycin, 2mM glutamine and 10% foetal bovine serum. THP-1 cells were seeded at $1x10^5$ cells/well/ml in RPMI-1640 medium containing penicillin/streptomycin, 2mM glutamine and 10% foetal bovine serum with 400ng/ml phorbol myristate acetate 4-6 days prior to assay. For the assay, the medium was decanted from the plates and they were washed with 1ml/well ice cold phosphate-buffered saline containing 2mg/ml BSA. Into the wells, add the following reagents (all in µl):

	NSB well	Bo well	Assay well
Assay buffer	100	150	100
Competing compound	-	-	50
NSB compound	50	-	-
[^{125}I]acLDL	50	50	50

The assay buffer was Dulbecco's minimal essential medium containing penicillin/streptomycin, 2mM glutamine and 2mg/ml bovine serum albumin. [^{125}I]acLDL used at 150,000cpm per well in assay (approx. 1.5µg/ml).

The plates were incubated for 3 hours at 37°C after which time the reagents were removed and the plates were washed with pre-chilled wash buffer (2: 0.15M NaCl, 50mM Tris-HCl, pH7.4). The plates were then incubated with pre-chilled wash buffer for 10 minutes on ice, and this step was then repeated. A further rapid wash was carried out with a different wash buffer (0.15M NaCl, 50mM Tris-HCl, pH7.4) before adding 500µl NaOH for 30 minutes at room temperature. The well contents were transferred to Sarstedt tubes for radioactivity counting on a Wallac 1480 Wizard automatic gamma counter.

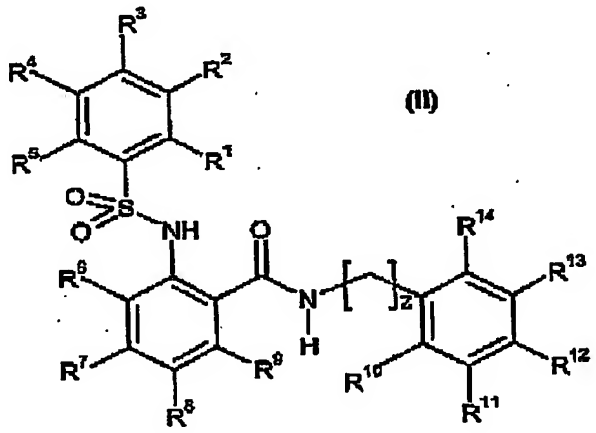
In order to assess cell coverage in the wells and show that cells were not lost during assay, 300µl of a 2% crystal violet stain in 95% methanol was added to the wells and incubated for 30 minutes at room temperature.

The IC50 for 4-bromo-N-(4-bromophenyl)-2-(3-chloro- 4-fluoro- phenylsulfonylamido) benzamide was found to be 25.9µM, and the chemically identical ^{18}F labelled version of the compound should produce a similar value. The IC50 for 4-bromo-N-(4-iodophenyl)-2-(4-chlorophenylsulfonylamido) benzamide was 25.2µM, and chemically identical radioiodinated versions of the compound should produce similar values.

Claims

1) An imaging agent which comprises a synthetic MSRA antagonist labelled with an imaging moiety, wherein the synthetic MSRA antagonist is a sulphonamidobenzamide compound, and wherein the imaging moiety can be detected externally in a non-invasive manner following administration of said labelled synthetic MSRA antagonist to the mammalian body *in vivo*.

2) The imaging agent of claim 1 wherein the sulphonamidobenzamide compound is of Formula (II):



(II)

wherein;

z is 0, 1 or 2;

R^1-R^{14} are independently R groups, where R is;

hydrogen, hydroxy, carboxy, C_{1-6} alkyl, nitro, cyano, amino, halogen, C_{6-14} aryl, alkenyl, alkynyl, acyl, aroyl, carboalkoxy, carbamoyl, carbamyl, alkysulphinyl, arylsulphinyl, arylalkylsulphinyl, alkylsulphonyl, arylsulphonyl, arylalkylsulphonyl, sulphamyl, arylsulphonamido or alkylsulphonamido.

3) The imaging agent of claim 2 wherein each R^1 to R^{14} is chosen from:

an imaging moiety, hydrogen, C_{1-6} alkyl, hydroxy, carboxy, amino or halogen.

4) The imaging agent of claims 2 and 3 wherein one of R^2, R^3, R^7, R^8 and R^{12} in Formula (II) is an imaging moiety, and the remaining R^2, R^3, R^7, R^8 and R^{12} groups are independently selected from hydrogen, C_{1-6} alkyl, carboxy, or a halogen selected from chlorine, bromine, fluorine or iodine.

5) The imaging agent of claims 2-4 wherein R^3, R^8 and R^{12} are each independently a halogen selected from chlorine, bromine, fluorine or iodine.

6) The imaging agent of claims 1-5 wherein said imaging moiety is selected from:

(i) a radioactive metal ion;

(ii) a paramagnetic metal ion;

(iii) a γ-emitting radioactive halogen;

(iv) a positron-emitting radioactive non-metal;

(v) a hyperpolarised NMR-active nucleus.

7) The imaging agent of claim 6, wherein the radioactive metal ion is a gamma emitter or a positron emitter.

8) The imaging agent of claim 7, wherein the radioactive metal ion is selected from ^{99m}Tc, ^{94m}Tc, ^{111}In, ^{113m}In, ^{64}Cu, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{48}V, ^{52}Fe and ^{55}Co.

9) The imaging agent of claim 6, wherein the paramagnetic metal ion is selected from paramagnetic ions of Gd, Mn and Fe.

10)The imaging agent of claim 7, wherein the paramagnetic metal ion is Gd(III).

11)The imaging agent of claim 6, wherein the γ-emitting radioactive halogen is a radioactive isotope of iodine.

12)The imaging agent of claim 11, wherein the radioactive isotope of iodine is chosen from ^{123}I or ^{131}I.

13)The imaging agent of claim 6, wherein the positron-emitting radioactive non-metal is selected from ^{11}C, ^{13}N, ^{15}O, ^{17}F, ^{18}F, ^{124}I, ^{75}Br and ^{76}Br.

14)The imaging agent of claim 13, wherein the positron-emitting radioactive non-metal is ^{18}F.

15)The imaging agent of claim 6 wherein the hyperpolarised NMR-active nucleus is selected from ^{13}C, ^{15}N, ^{19}F, ^{29}Si and ^{31}P.

16)The imaging agent of claim 15 wherein the hyperpolarized NMR-active nucleus is ^{13}C.

17)The imaging agent of claims 6-10, wherein the imaging moiety is a radioactive or a paramagnetic metal ion and the metal ion is attached to the MSRA antagonist as part of a metal complex to form a conjugate of Formula (III):

[{MSRA antagonist}-$(L)_x$]$_y$-[metal complex] (III)

wherein:

$(L)_x$ is a linker group wherein;
each L is independently $-CZ_2-$, $-CZ=CZ-$, $-C\equiv C-$, $-CZ_2CO_2-$, $-CO_2CZ_2-$, -NZCO-, -CONZ-, -NZ(C=O)NZ-, -NZ(C=S)NZ-, $-SO_2NZ-$, $-NZSO_2-$, $-CZ_2OCZ_2-$, $-CZ_2SCZ_2-$, $-CZ_2NZCZ_2-$, a C_{4-8} cycloheteroalkylene group, a C_{4-8} cycloalkylene group, a C_{8-12} arylene group, or a C_{3-12} heteroarylene group; and
Z is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl;
x is an integer of value 0 to 10; and
y is 1, 2 or 3.

18)The imaging agent of claim 17 wherein the metal complex is a coordination complex of the radioactive metal ion or the paramagnetic metal ion with one or more ligands.

19)The imaging agent of claim 18 wherein said one or more ligands are chelating agents selected from diaminedioximes, N_3S ligands, N_2S_2 ligands, N_4 ligands and N_2O_2 ligands.

20)An imaging agent precursor of Formula (IIIa):

[{MSRA antagonist}-$(L)_x$]$_y$-[ligand] **(IIIa)**

wherein:
$(L)_x$ is a linker group wherein L is as defined in claim 17;
x is an integer of value 0 to 10; and
y is 1, 2 or 3.

21)A pharmaceutical composition comprising the imaging agent of claims 1-19 together with a biocompatible carrier, in a form suitable for mammalian administration.

22)The pharmaceutical composition of claim 21 for use in the diagnostic imaging of cardiovascular disease.

23)The pharmaceutical composition of claims 21 and 22 for use in the diagnostic imaging of atherosclerotic plaques, coronary artery disease, thrombosis, transient ischaemia or renal disease.

24)The pharmaceutical composition of claim 23 for use in the diagnostic imaging of atherosclerotic plaques.

25)The pharmaceutical composition of claim 24 for use in the diagnostic imaging of unstable atherosclerotic plaques.

26)A kit for the preparation of the pharmaceutical composition of any of claims 21-27 comprising a precursor of the imaging agent of any of claims 1-19.

27)The kit of claim 26 wherein said precursor is of Formula (IIIa) of claim 20.

28)The kit of claim 27 wherein the preparation of said pharmaceutical composition comprises reaction of a radioactive metal ion or a paramagnetic metal ion with the precursor of Formula (IIIa).

29)The kit of claim 28 wherein the radioactive metal ion is selected from ^{99m}Tc, ^{111}In, ^{64}Cu, ^{67}Cu, ^{67}Ga and ^{68}Ga.

30)The kit of claims 28 and 29 wherein the radioactive metal ion is ^{99m}Tc.

31)The kit of claim 28 wherein the paramagnetic metal ion is selected from Gd, Mn and Fe.

32)The kit of claim 31 wherein the paramagnetic metal ion is Gd(III).

33)Use of the imaging agent of claims 1-20 for the diagnostic imaging of cardiovascular disease.

34)The use of claim 33 wherein the cardiovascular disease is atherosclerosis.

Abstract

The present invention is in the field of diagnostic imaging. In one aspect, the invention relates to novel imaging agents comprising synthetic macrophage scavenger receptor A antagonists, said imaging agents being useful in the diagnostic imaging of cardiovascular disease. Also claimed in the present invention is a pharmaceutical composition comprising the novel imaging agents of the invention, said pharmaceutical composition being useful for the diagnostic imaging of cardiovascular disease in humans. Another aspect of the present invention is a kit useful in the preparation of the pharmaceutical composition of the invention. Furthermore, the use of the imaging agent of the invention for the diagnostic imaging of cardiovascular disease is also claimed.

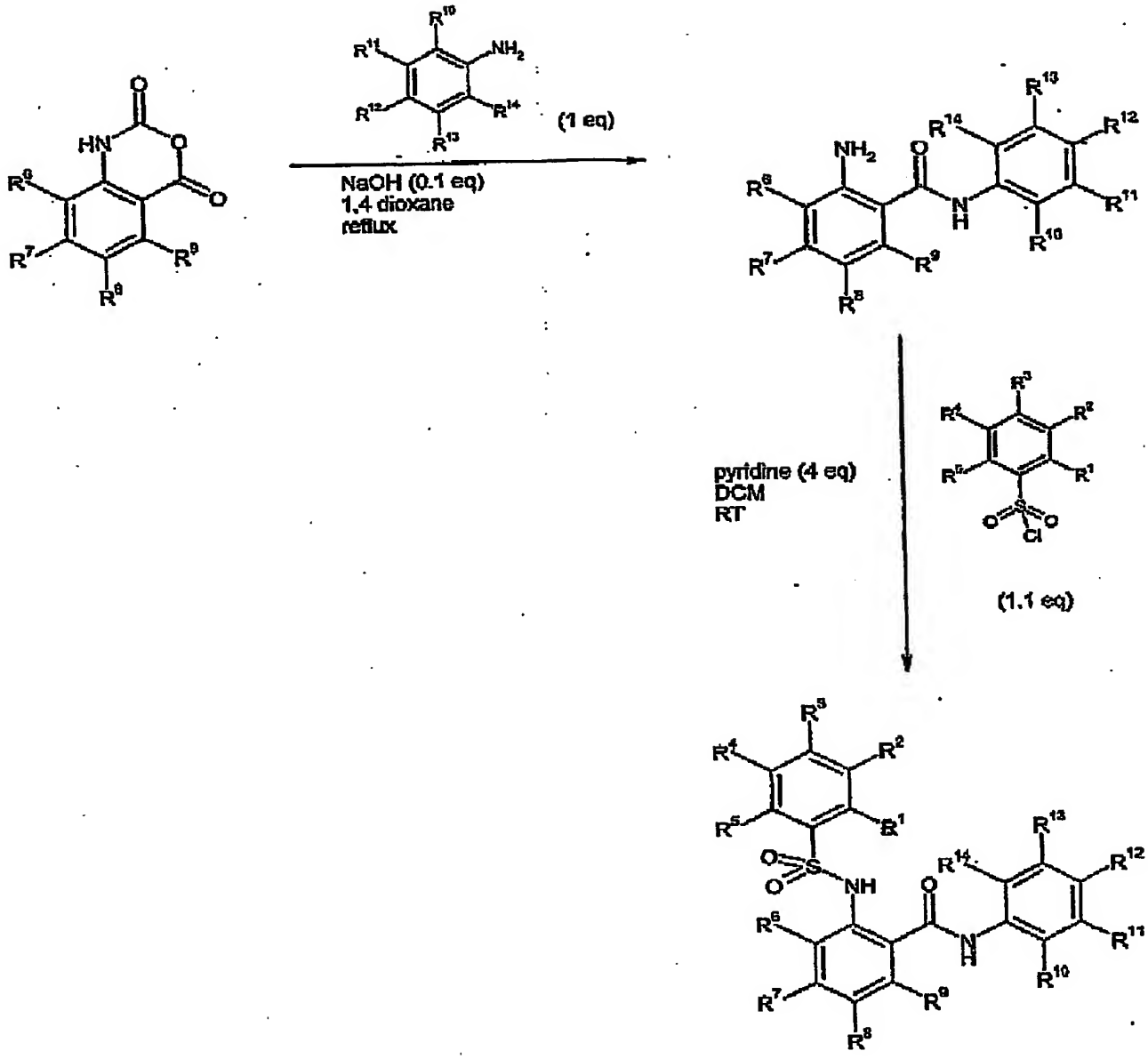


Figure 1

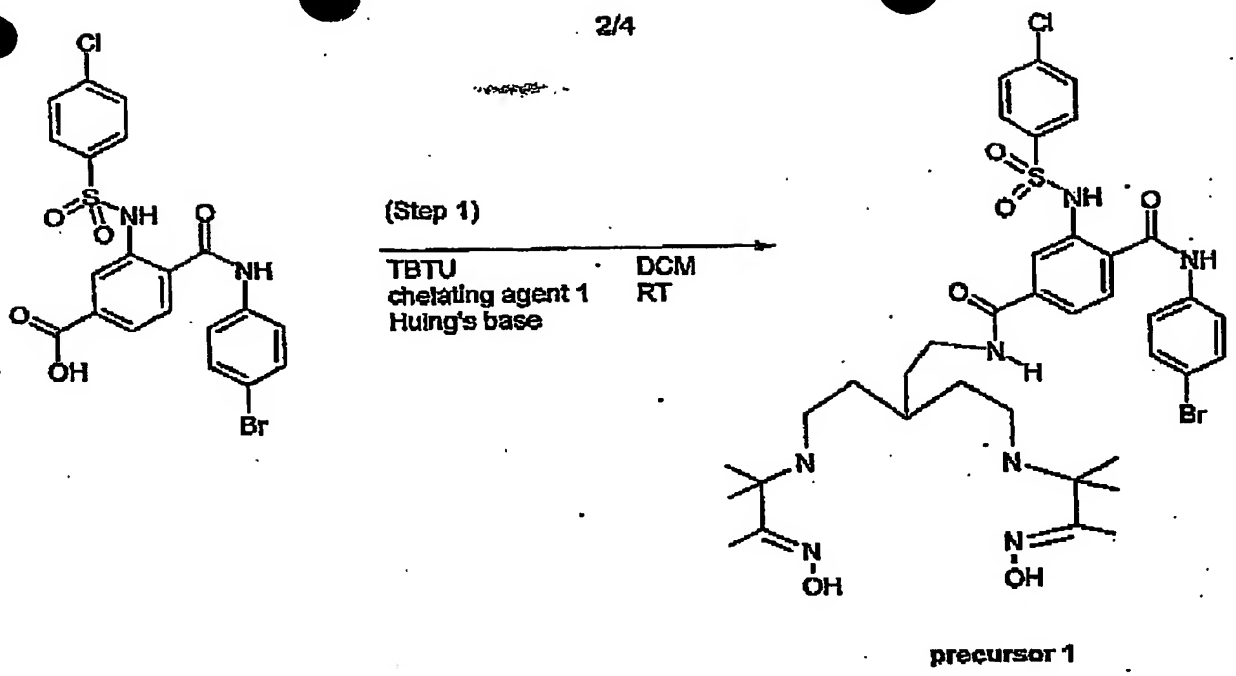

(Step 1)
TBTU
chelating agent 1
Huing's base
DCM
RT
precursor 1
TcO_4
$SnCl_2$/MDP
37°C
(Step 2)
imaging agent 1
99m

Figure 2

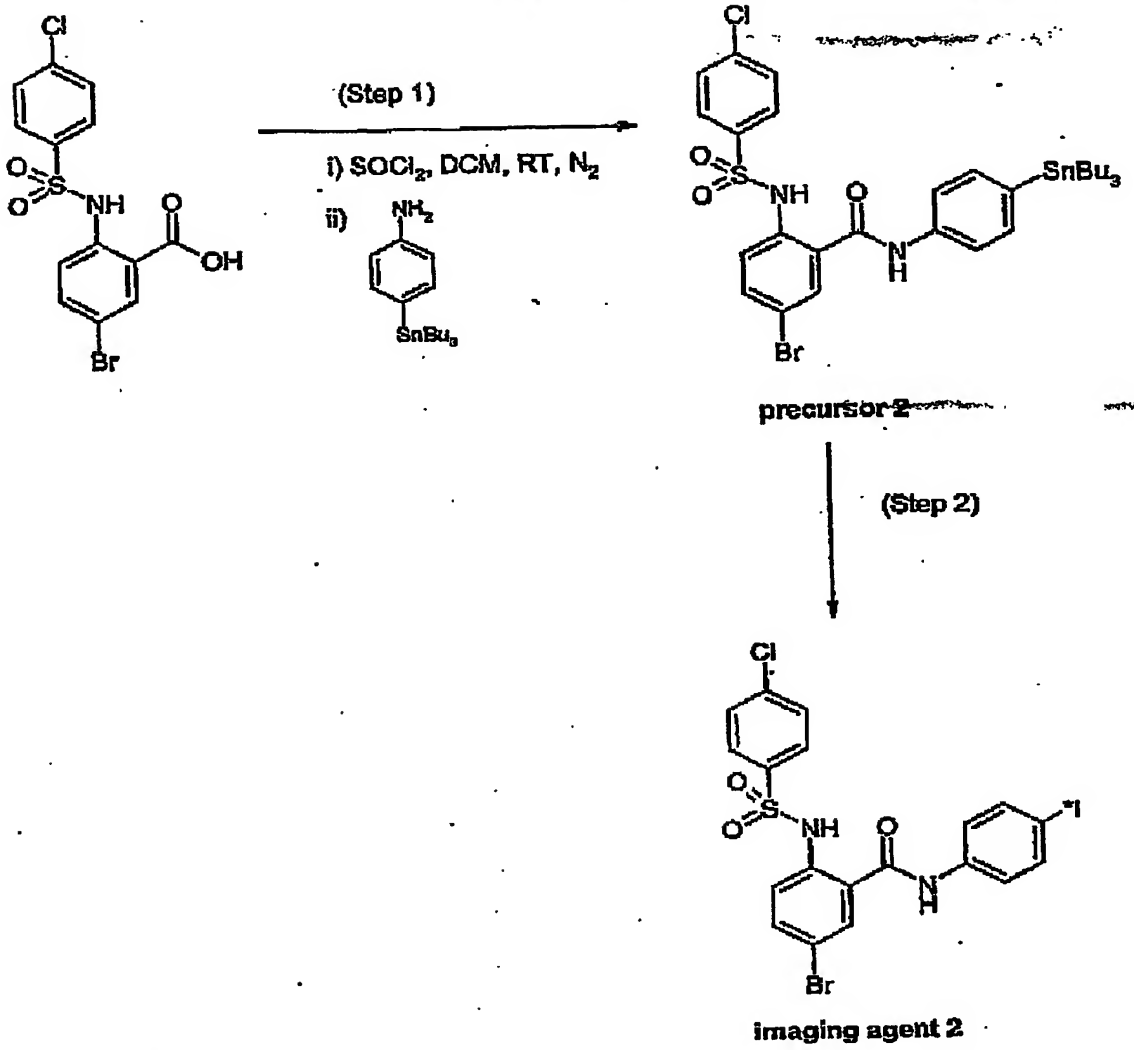

Cl
(Step 1)
i) $SOCl_2$, DCM, RT, N_2
ii)
NH_2
$SnBu_3$
Cl
$SnBu_3$
Br
precursor 2
(Step 2)
Cl
*I
Br
imaging agent 2

Figure 3

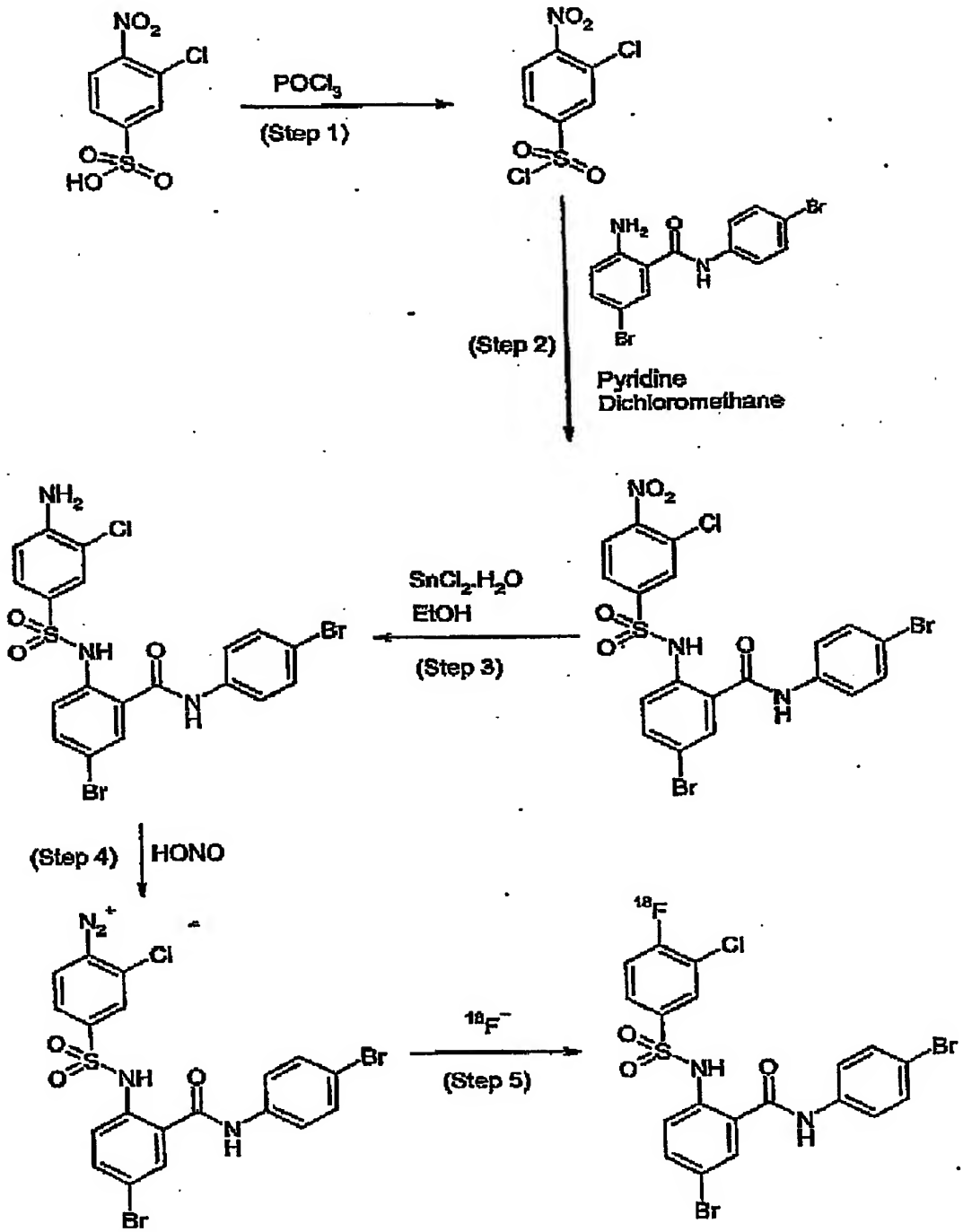

NO2
Cl
POCl3
(Step 1)
HO
O
S
O
NH2
Br
(Step 2)
Pyridine
Dichloromethane
SnCl2.H2O
EtOH
(Step 3)
(Step 4)
HONO
N2+
18F
18F−
(Step 5)

Figure 4